

Continuous monitoring of membrane lung carbon dioxide removal during ECMO

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**Continuous Monitoring of Membrane Lung Carbon Dioxide Removal During ECMO:
Experimental Testing of a New Volumetric Capnometer**

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**Continuous Monitoring of Membrane Lung Carbon Dioxide Removal During ECMO:
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ABSTRACT

Background: ECMO constitutes a complex support modality, and accurate monitoring is required. An ideal monitoring system should promptly detect ECMO malfunctions and provide real-time information to optimize the patient-machine interactions. We tested a new volumetric capnometer which enables continuous monitoring of membrane lung carbon dioxide removal ($V'\text{CO}_2\text{ML}$), to help in estimating the oxygenator performance, in terms of CO_2 removal and oxygenator dead space (VDsML).

Methods: The current study was conducted on 9 pigs undergoing veno-arterial ECMO due to cardiogenic shock after induced acute myocardial infarction. The accuracy and reliability of the prototype of the volumetric capnometer ($\text{CO}_2\text{RESET}^{\text{TM}}$, by Eurosets srl, Medolla, Italy) device was evaluated for $V'\text{CO}_2\text{ML}$ and VDsML measurements by comparing the obtained measurements from the new device to the standard method with the use of a standard capnometer and the sweep gas values. Measurements were taken at five different levels of gas flow/blood flow ratio (0,5-1,5). The agreement between the corresponding measurements taken with the two methods was assessed. We expected that 95% of differences was between $d-1.96s$ and $d+1.96s$.

Results: 120 coupled measurements from each device were obtained for the $V'\text{CO}_2\text{ML}$ calculation and 40 for the VDsML . The new capnometer mean percentage bias (95% CI of limits of agreement) was 3.86% (12.07 – 4.35%) for $V'\text{CO}_2\text{ML}$, and 2.62% (8.96 – 14.20%) for VDsML . A negative proportional bias for $V'\text{CO}_2\text{ML}$ estimation with the new device was observed with a mean of 3.86% (12.07 – 4.35%). No correlations were found between differences in the coupled $V'\text{CO}_2\text{ML}$ and VDsML measurements and the gas flow/blood flow ratio or temperature. Coupled measurements for $V'\text{CO}_2\text{ML}$ showed a strong correlation ($r_s=0.991$; $p=0.0005$), as did VDsML calculations ($r_s=0.973$; $p=0.0005$).

Conclusion: The volumetric capnometer is reliable for continuous monitoring of CO_2 removal by ML and VDsML calculations. Further studies are necessary to confirm these data.

Keywords: Capnometer, Membrane Lung Carbon Dioxide Removal, Extracorporeal Membrane Oxygenation monitoring, Oxygenator performance, Membrane Lung Function, $V'\text{CO}_2$, ECMO, ECLS

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Background

In recent years, there has been a significant increase of extracorporeal membrane oxygenation (ECMO) utilization for both cardiac (VA-ECMO) and respiratory (VV-ECMO) support¹. However, ECMO is a complex system that requires prompt changes in its settings on the basis of the rapid variations of the patients' conditions. Accurate monitoring of vital body parameters is, therefore, a key factor for the early detection of complications and the proper management of the cardiac and respiratory support ². Thus, an optimal monitoring equipment should provide information regarding the pump function as revolution per minute (rpm), blood flow (l/min), inlet and outlet pressures (mmHg) and the membrane lung performance ³. Evaluation of the membrane lung (ML) performance is of paramount importance during ECMO not only because it might indicate a gradual or sudden functional impairment and therefore the need and the timing for the membrane lung replacement due to clot formation inside the oxygenator, but may also provide information regarding both the native lung (NL) and the ML contribution to the global ventilation, hence guiding the weaning process⁴.

Furthermore, as for the NL, the ML performance is assessed by measuring both the O₂ transfer (V'O₂ML) and CO₂ removal (V'CO₂ML) through the oxygenator.

Whilst some devices applied to the ECMO circuits already allow for continuous monitoring of V'O₂ML, there are only two systems currently available for the continuous monitoring of V'CO₂ML. However, the continuous evaluation of CO₂ removal by ML (V'CO₂ML) is extremely important since it also allows the ML dead space calculation (VDsML), which can be altered due to clot formation inside the oxygenator and fibres oedema (as the plasma leakage phenomenon). In this situation, fractions of the ML are ventilated but not perfused, hence they do not participate in the CO₂ removal. Moreover, a continuous measurement of the CO₂ removed by the oxygenator allows a more precise distinction between the different contributions of both the patient and the oxygenator to the global ventilation and, hence, provide significant information during weaning from the ECMO machine. Moreover, a continuous monitoring of CO₂ percentage in the exhaust gas could be used as an alarm of gas flow failure or disconnection.

In our experimental study, we tested the accuracy and the reliability of a new volumetric capnometer which enables continuous monitoring of $V'CO_2ML$ by the direct measurement of the CO_2 partial pressure at the exhaust gas port of the membrane lung (%) and the gas flow (l/min), The and to calculate the dead space during ECMO.

Methods

The current animal model experiment was conducted at the University Hospital of Maastricht, The Netherlands on nine pigs undergoing veno-arterial ECMO (VA ECMO). The protocol was approved by the ethical committee of the University Hospital of Maastricht (protocol number WP 2015-003-001).

The pigs were anaesthetized, intubated, ventilated by constant ventilator settings. The present study was conducted as part of a major one aimed at comparing the effects of treatments alone with VA ECMO in addition to IABP (intra-aortic balloon pump) in pigs in cardiogenic shock. Such a condition was obtained by inducing an acute myocardial infarction (left anterior descending coronary artery ligation), and, after four hours of monitoring, the two capnometers were tested. The tubing set and the ECMO oxygenators (model "adult ECMO 14 days") were provided by Eurosets srl, Medolla, Italy. In more details, we evaluated the accuracy and reliability of a prototype of a new volumetric capnometer device (CO_2RESET^{TM} , Eurosets srl, Medolla, Italy) that provide directly and continuously the $V'CO_2ML$ values and the $VDsML$ calculation, by comparing the obtained measurements with the new device to the ones obtained with a standard method.

The standard method used a normal capnometer (Microcap Plus®Capnograph, Medtronic, Minneapolis, Minnesota, USA) which was routinely used in clinics for measurements of the CO_2 concentration in the exhaled air of the patient (the end-tidal CO_2 , expressed as %) and the values of gas flow displayed on the standard gas blender.

We measured $V'CO_2ML$ and $VDsML$ at five different levels of gas flow/blood flow ratio (0,5-1,5) and we obtained three $V'CO_2ML$ measurements for each level of gas flow/blood flow ratio (in total, 135 couples of values expected), while only one for the $VDsML$ at each level of gas flow/blood flow (in total, 45 couples of values expected). We performed a blood gas analysis at each level of gas

flow/blood flow to obtain the inlet blood pCO₂ and the outlet blood pCO₂. Moreover, we also continuously recorded both pigs' body and exhaust gas temperatures.

Devices Characteristics:

The new device consists of a mid-range infrared sensor placed mainstream (compared to the standard device with side-stream sampling) to the oxygenator exhaust connector, combined with a flow sensor device placed at the oxygenator gas inlet (Figure 1). The CO₂ concentration is calculated on the basis of the radiation variation caused by the CO₂ absorption characteristics, as with the common capnometers. However, not only does the combination of the capnometer and the flowmeter allows the continuous evaluation of the percentage of CO₂ exhaust by the ML, but also the continuous V'CO₂ML calculation. Furthermore, a system placed inside the capnometer maintains the temperature of the gas exhaust between 40-42°C, avoiding condensation as well as misleading measurements. Ultimately, a dedicated software tool calculates the measurements and shows CO₂ [%], CO₂ [mmHg], inlet gas flow [l/min] and V'CO₂ML [ml/min].

The standard hand-held capnometer is a clinically validated device for measuring the CO₂ concentration in patient exhaled gases. It works with an internal sensor (based on radiation absorption technology) by sampling the gases from the exhaust gas port of the oxygenator through a narrow tube. It is possible to calculate intermittently the V'CO₂ML combined the CO₂ percentage obtained by the standard capnometer with the contemporary value of sweep gas set on the gas blender.

V'CO₂ML and Dead Space Monitoring

While the CO₂ concentration in the exhaust gas (%CO₂) from the ML and V'CO₂ML were directly shown on the screen by "CO2RESET™" capnometer's software, the value of V'CO₂ML derived from the measured %CO₂ with the second method was calculated as follows

$$V'CO_2ML [ml/min] = \%CO_2 \times GF [l/min] \times 10$$

where GF is the gas flow, %CO₂ is the concentration as percentage of CO₂ in exhaust gas, and V'CO₂ML is the membrane lung carbon dioxide removal.

In addition, the two methods were compared for the dead space calculation, which was obtained by the following equation:

$$VD_{sML} [\%] = \frac{100 (pCO_2 \text{ out } [mmHg] - \%CO_2)}{pCO_2 \text{ out } [mmHg]}$$

where the VD_{sML} is the membrane lung dead space, the $pCO_2 \text{ out}$ is the carbon dioxide partial pressure into the outlet blood, and the $\%CO_2$ is the concentration of carbon dioxide in the gas sampled at the exhaust gases port of the oxygenator.

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24, IBM Corporation 2015, Armonk, NY.

The correlations between all the obtained measurements with the new volumetric capnometer and the ones obtained with the standard method (Microcap Plus®Capnograph, Medtronic, Minneapolis, Minnesota, USA) were calculated using the Spearman correlation coefficient. A level of $P < 0.05$ was chosen to indicate statistical significance.

The Bland-and-Altman⁵ method was used to evaluate the agreement between the measurement taken with the standard and new methods, after assessing the normal distribution of the differences. The lack of agreement was summarized by calculating the bias, estimated by the mean difference (d) and the standard deviation of the differences (s). We expected that 95% of differences was between $d - 1.96s$ and $d + 1.96s$.

Results

We obtained 120 coupled measurements for each method suitable for the $V'CO_2ML$ calculation and 40 coupled measurements suitable for the VD_{sML} calculation. Because of a failure of the capnometer's heater system, the data recorded by one animal were judged potentially not reliable and not included.

As seen in Figures 2a-2b, we observed a strong correlation between the measurements of $V'CO_2ML$, ($r_s=0.991$; $p=0.0005$) taken with the volumetric capnometer, and those obtained with the standard method. Moreover, the volumetric capnometer showed a low mean percentage bias for $V'CO_2ML$ measurements at exactly 3.86% (12.07 – 4.35%).

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Regarding the dead space calculation, not only did we observed a significant ~~strong~~ correlation between the two methods for VDsML calculation ($r_s=0.973$; $p=0.0005$), but we also identified a very low mean percentage bias with the volumetric capnometer at 2.62%(8.96 – 14.20%), as it can be seen in Figures 3a-3b.

In addition, although a negative proportional bias for V'CO₂ML estimation with the volumetric capnometer was observed, such underestimation in the lower range of V'CO₂ML was less than 4%, which represents an acceptable limit for clinical setting.

Moreover, we investigated whether variations in gas temperature and gas flow/blood flow ratio could have affected the differences in the coupled measurements obtained with the two devices. In this regard, we found no significant correlations between the difference in the coupled V'CO₂ML and VDsML measurements for either the gas flow/blood flow ratio or temperature.

Finally, Figure 4 shows the variation of VDsML at increasing gas flow/blood flow ratios. As it can be observed, increasing gas flow/blood flow ratios (increased ventilation per unit of blood) correspond to higher values of VDsML. This can be explained by the fact that the increase in the ventilation per unit of blood implies a corresponding increase in the ventilation per mm² of oxygenator's membrane up to a certain threshold, which is determined by the permeability properties of the membrane. Once the threshold has been reached, a further increase in ventilation will create an increase in dead space (in series).

Discussion

In the present study, we evaluated the accuracy and reliability of a new volumetric capnometer which allows the continuous V'CO₂ML monitoring and VDsML calculation thanks to its two components. The flowmeter was placed in series to the sweep gas line, and the capnometer was positioned at the exhaust gas port of the oxygenator.

ECMO constitutes a life-saving mechanical support which often requires accurate monitoring and potentially prompt interventions because of either variation in patient clinical conditions, the occurrence of possible complications, or ECMO system malfunction. Thus, an appropriate and continuous monitoring of gas exchange inside the oxygenator is useful in order to evaluate both the

ML performance and to distinguish between the ML and native lungs (NL) ventilation². Currently, data regarding ML gas exchange are usually obtained by taking blood samples by the ECMO circuit added to the volumetric capnometry of the ML during the routinely ECMO check at least daily. However, due to the complexity of the support machine, of the patient-machine interactions, together with the high risk of system-related complications during prolonged use, there could be a great benefit by the use of an on-line monitoring system which can provide real-time information regarding both the ML and pump performances. In fact, the study of the trend in the $V'CO_2ML$ permits to avoid bias related to the specific moment in which the single measurement has been taken, constituting a more reliable tool. Hence, we believe that the continuous monitoring of both CO₂ removal and ML dead space with the volumetric capnometer allows a better timing for the detection of ML dysfunction and can potentially guide the ECMO weaning process by integrating ML and mechanical ventilator information.

In addition, with regards to the patient complications related to ECMO use, it is reported that ML failure constitutes the second most common mechanical complication.⁶ Moreover, despite the advent of new ML coated with a tip-to-tip antithrombotic surface coating, the interactions of blood with non-biological surfaces boost the systemic inflammatory response and lead to clotting within the ML⁷. Such deposits are responsible for the worsening of ML gas exchanges because of an increased dead space inside the oxygenator and, hence, of an increased proportion of ventilated but not perfused areas. Therefore, we believe that the continuous evaluation of the $V'CO_2ML$ other than the dead space not only can highlight an ML performance reduction, but also guide the ML replacement timing. For instance, providing that ML replacement does not constitute a no-risk procedure in those patients, the $V'CO_2ML$ evaluation could allow a monitored delay in its replacement, whenever the CO₂ clearance is sufficient for the patient's clinical needs.

In addition, discontinuing extracorporeal respiratory support is another crucial step in ECMO patient management, and it often constitutes a difficult decision, mainly due to the lack of definite criteria. Mols et al.⁸ indicated the successful weaning from the ECMO machine when at least 80% of total oxygen delivery was supplied by the patient's own lung⁸. Similarly, Grasselli et al.⁹ suggested that respiratory mechanics and patient blood gases should also be considered in the decision of ECMO

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withdrawal. On the other hand, we previously reported how the combined evaluation of $V'CO_2ML$ and VCO_2NL obtained by the volumetric capnometry function integrated in the modern ventilators could provide additional information regarding the NL recovery such as improvements in its CO_2 clearance capability¹⁰. In our opinion, in fact, in order to estimate the residual function of the NL more accurately, clinicians should analyse not only the oxygenation function ($V'O_2ML$) of the ML, but also the extracorporeal CO_2 removal ($V'CO_2ML$). Thus, the continuous $V'CO_2ML$ monitoring by the new volumetric capnometer could potentially help in analysing NL/ML interaction, guiding the ECMO weaning process and choosing the best timing for the ECMO discontinuation³.

Conclusions

In conclusion, our experimental study demonstrates that the volumetric capnometer used in conjunction with the ECMO oxygenator is reliable for continuous monitoring of $V'CO_2$ and useful for oxygenator dead space calculation, as the measurements obtained with a standard method by a normal capnometer. Moreover, we believe that the information provided by such a device are helpful in order to promptly detect oxygenator malfunction and its impaired performance in terms of CO_2 removal. Furthermore, if these monitoring approach will be confirmed in future studies, the $V'CO_2ML$ continuous monitoring could help to better guide ECMO weaning and improve the the patient management. Further studies are vital in order to confirm our results in a clinical setting.

List of abbreviations:

BF: blood flow

ECMO: extracorporeal membrane oxygenation

ML: membrane lung

NL: native lung

$p\text{CO}_{2,\text{out}}$: CO_2 blood partial pressure in the outlet blood from oxygenator

VA ECMO: veno-arterial extracorporeal membrane oxygenation

$\text{VCO}_{2\text{NL}}$: CO_2 removal through the Native Lung

$\text{V}'\text{CO}_{2\text{ML}}$: CO_2 removal through the Membrane Lung

$\text{V}'\text{O}_{2\text{ML}}$: O_2 transfer through the Membrane Lung

VDsML : Membrane Lung dead space

VV ECMO: veno-venous Extracorporeal Membrane Oxygenation

$\%\text{CO}_2$: concentration (%) of carbon dioxide in exhaust gas

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Declarations:

Ethics approval:

The current animal model experimental protocol was approved by the ethical committee of the University Hospital of Maastricht (protocol number WP 2015-003-001).

Availability of data and materials:

The analysed dataset is available from the corresponding Author on reasonable request.

Declaration of Conflicting Interests:

MB is advisor, speaker at congress and meetings, external independent scientific reviewer for Eurosets srl (Medolla, Italy) and Hamilton Medical (Bonaduz, CH) and congress and meeting speaker for Getinge Group A.B. (U.S.A.), Estor Italia and MSD Italy.

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Authors' contribution: MB designed the study protocol. AM, OP, SG, SN, MM, FM, MDJ, DMJ and RL conducted the experiments. AM and OP carried out analysis. AM, MB, DMJ and RL contributed to drafting and writing the manuscript. All authors read and approved the final manuscript.

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Legends to the Figures

Figure 1: the new volumetric capnometer is applied to the ECMO machine; at the top in the red circle the flowmeter, and at the bottom in the red circle the capnometer.

Figure 2: panel a. Correlation between the $V'CO_2ML$ values obtained with the volumetric capnometer with the values calculated with the standard method; **panel b.** Mean bias and precision of $V'CO_2ML$ values obtained with the volumetric capnometer compared to the values calculated with the standard method

Figure 3: panel a. Correlation between the values of $VDsML$ obtained by new volumetric capnometer versus the values calculated with the standard method ; **panel b.** Mean bias and precision of $VDsML$ values obtained with the volumetric capnometer compared to the values calculated with the standard method.

Figure 4: Scatter plot showing the values of the $VDsML$ measured by the two methods at five different levels of BF/GF ratio. These data show that the increasing of gas BF/GF ratios corresponds to an increase of the $VDsML$ values, as consequence of the overcome capacity of the ML membrane in terms of CO_2 elimination.

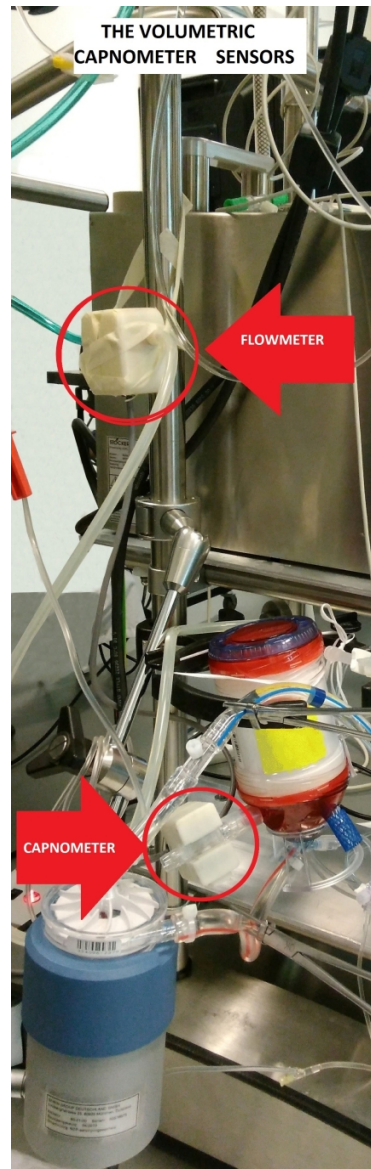


Figure 1

301x950mm (96 x 96 DPI)

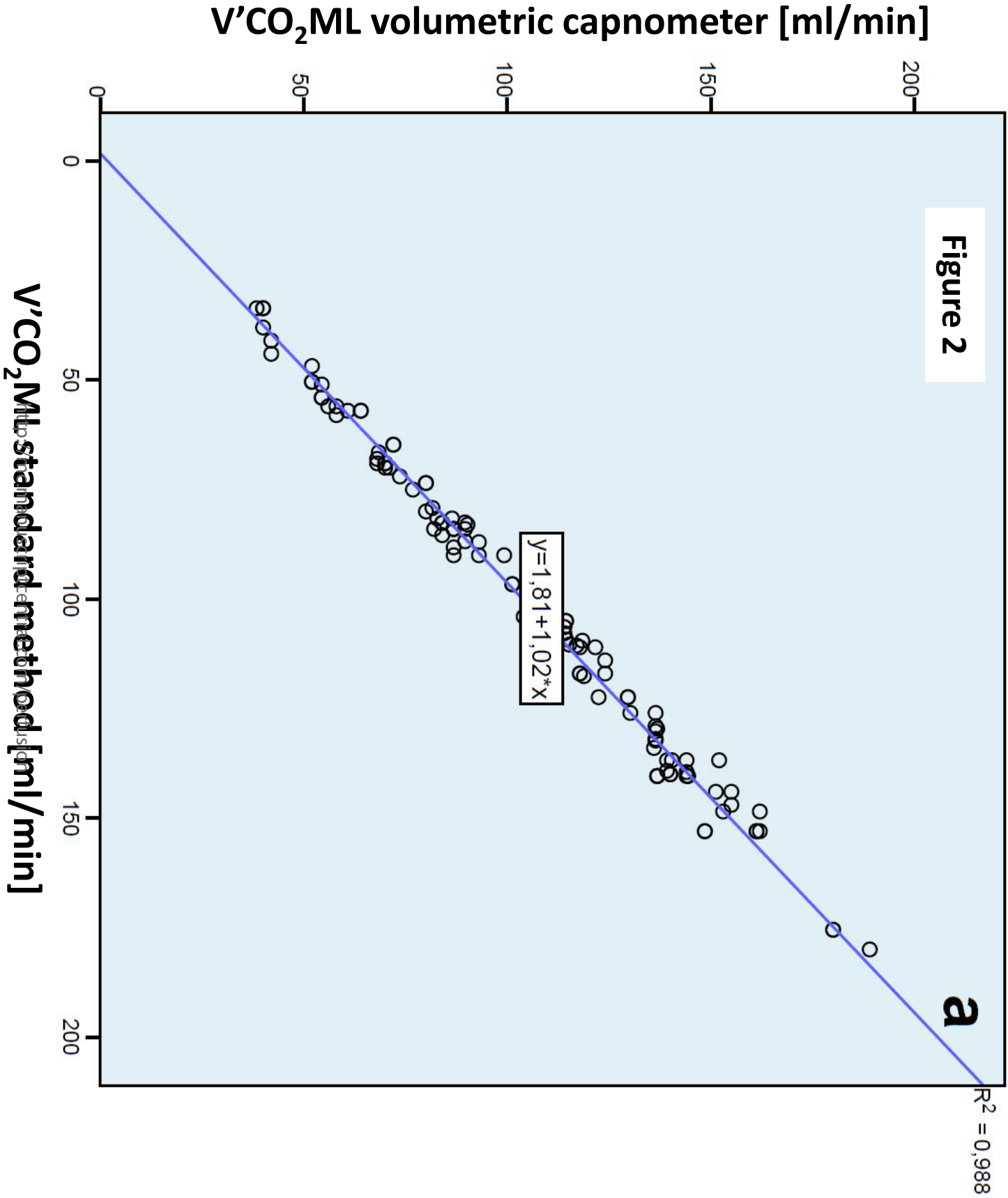
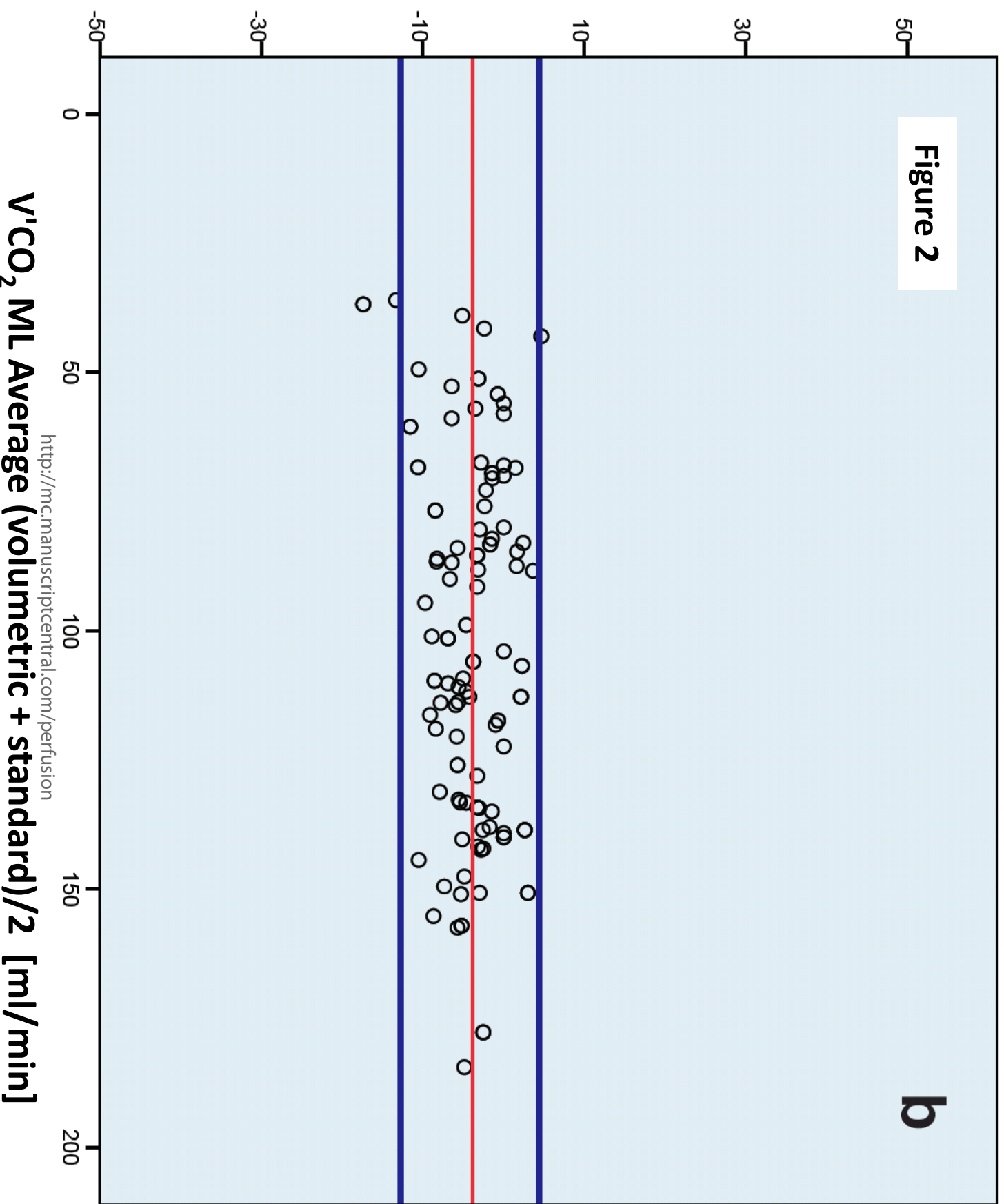


Figure 2

b

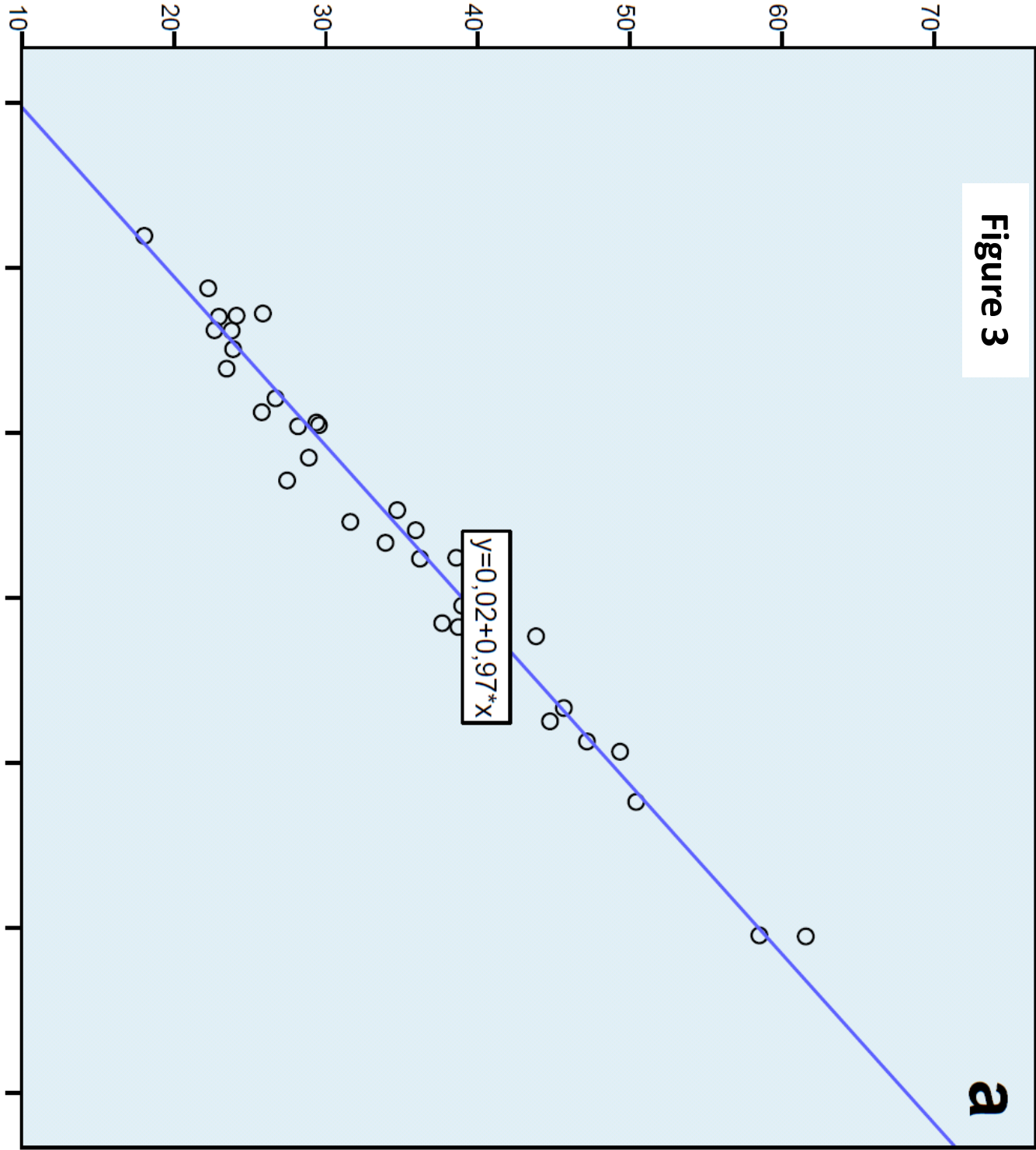
 $V'\text{CO}_2\text{ML Difference } [\%]$ 

<http://mc.manuscriptcentral.com/perfusion>

Figure 3

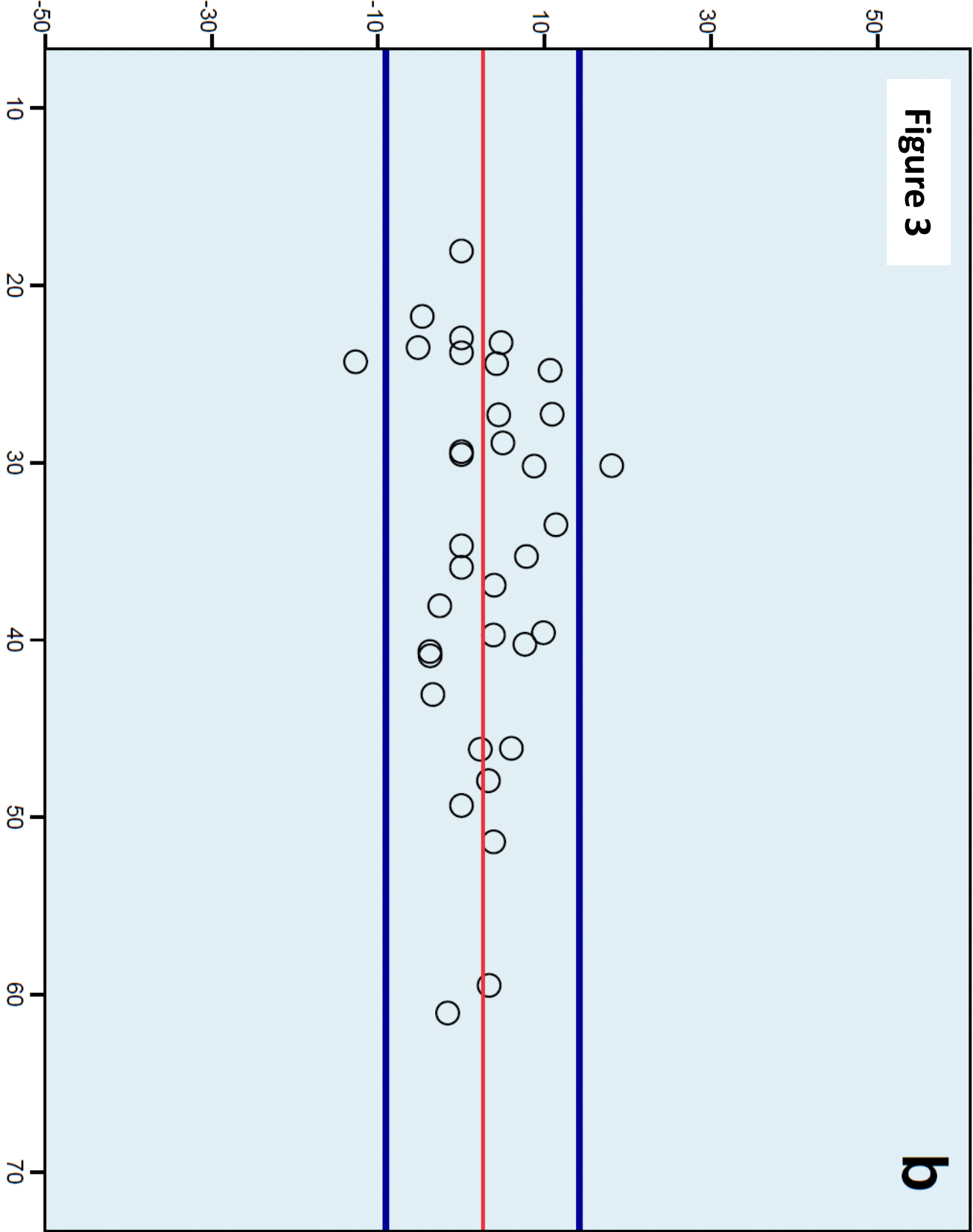
a
 $R^2 = 0,971$

VDsML volumetric capnometer [ml]



<http://mc.manuscriptcentral.com/perfusion>

VDsML standard method [ml]



<http://mc.manuscriptcentral.com/perfusion>
VDsML Average (Volumetric + standard)/2 [ml/min]

Figure 4

